Training the “Mathematical Brain”: evidence from functional brain imaging and neuro-modulation techniques
Overview

**Neuro-imaging techniques**
functional Magnetic Resonance Imaging (fMRI)

Multivariate approaches

**Neuro-modulation techniques**
transcranial Direct Current Stimulation (tDCS)

**Neuro-rehabilitation**

**Brain Plasticity**
Biomarkers
Learning
Brain Organization
Individual Differences

*Developmental Dyscalculia*
Developmental Dyscalculia

- Neurodevelopmental learning disability
- 3 to 7% of individuals
- Difficulties in dealing with numbers and performing arithmetic
- Significant effects on educational and social outcomes
- Crucial to intervene to alleviate poor performance in these learners
Introduction

- Classroom-based and individual-based **behavioral training** could be effective, yet the **neurobiological mechanisms** underlying successful intervention are **unknown** (Dowker et al., 2004; Fuchs et al., 2008, 2009, 2013)

- **Math learning** is supported by a **host of brain systems** including those serving numerical, mnemonic, visuo-spatial and executive functions

- **Developmental Dyscalculia (DD)** has been characterized as a condition reflecting **structural** and **functional brain abnormalities** (Butterworth, 2011, Fias et al., 2014)

- Uncovering **brain plasticity effects** by tracking the **functional brain changes** following effective intervention **could inform on**:

  (i) which **aspects of cognition** are **impaired** in DD during math problem solving,

  (ii) which of these **mechanisms** could be **strengthened** as a result of intervention
Research Questions

1. Can 8 weeks of math tutoring remediate behavioral performance in DD?

2. Can 8 weeks of math tutoring elicit neuroplasticity effects in DD?

3. If neuroplasticity effects occur, would their signature be characterized by: (i) neural normalization, or (ii) neural compensation?

4. Is there a systematic relation between tutoring-induced neuroplasticity and behavioral improvement, if any, in DD?
Multi-criteria diagnosis of DD: (i) *Normed-based cut-off criterion*; (ii) *Discrepancy criterion*

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<th>TD (N = 15)</th>
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Introduction

Methods and Material

8 weeks of one-to-one math tutoring

**fMRI, sMRI**

Arithmetic task

**Math problem solving**

Addition trial

5 + 9 = 14

Control trial

4 = 4

Fixation

9.5 secs

Facilitate arithmetic fluency and strengthening number knowledge (Fuchs et al., 2008, 2009, 2013)

**MATH GAMES**

Math Bingo

“Find the answer on the Bingo card”

5 + 5

Math War

5 9 8 7

Treasure Hunt

3 + 4

Facilitate arithmetic fluency and strengthening number knowledge (Fuchs et al., 2008, 2009, 2013)

3 times per week

40-50 min

**Math problem solving**

**fMRI**

**fMRI, sMRI**

Arithmetic task

Study 1

Iuculano et al., under review; Supekar et al., 2013
Following 8 weeks of 1:1 tutoring children with DD showed significant performance improvement in math problem solving.
Results – Behavioral performance

Performance normalization in DD. Group-differences in performance before tutoring were no longer evident after tutoring.
Before tutoring children with DD showed over-activation in multiple brain areas of the Prefrontal Cortex (PFC), Posterior Parietal Cortex (PPC), Ventral Temporal-Occipital Cortex (VTOC) and Medial Temporal Lobe (MTL).

No brain areas showed higher activation after tutoring in DD.
Results – Functional normalization

Before tutoring, children with DD showed over-activation in multiple brain areas of the PFC, PPC, VTOC and MTL, compared to TD children.

After tutoring, no differences were evident between DD children and their TD control peers.
We asked whether functional activity patterns during arithmetic problem solving could be used to **discriminate** the brains of DD children from those of TD children **before** and **after** tutoring.

Functional activity patterns during arithmetic problem solving were sufficient and significantly able to **accurately discriminate** children with DD from TD children **before tutoring**, but not **after tutoring**, where the algorithm performed worse than chance.
Brain Plasticity Index (BPI) = Multivariate spatial correlation between pre- and post- tutoring activity patterns in DD

Does BPI relate to better performance gains in DD?

Yes, the more the brain changes, the better the performance in DD

None of the domain-general standardized measures (IQ, WM), nor math standardized measures significantly predicted performance improvement in DD.

Iuculano et al., under review
1. Can **8 weeks** of math **tutoring** remediate behavioral performance in DD?

   *Yes,* consistent with previous classroom-based studies, math tutoring focused on conceptual knowledge and speeded practice *can remediate poor math performance* in children with **DD**

2. Can **8 weeks** of math **tutoring** elicit **neuroplasticity effects** in DD?

   *Yes,* 8 weeks of **effective behavioral tutoring** *can elicit* neuroplasticity effects in children with **DD**

   **Tutoring-related effects** were evident *in multiple brain systems* supporting the hierarchical cascade of cognitive computations necessary for successful math problem solving

3. If **neuroplasticity** effects occur, **would their signature be characterized by:** (i) **neural normalization,** or (ii) **neural compensation**?

   Neuroplasticity effects support the **neural normalization** hypothesis: *prominent differences between the groups were evident* - in an univariate as well as multivariate sense – *before but not after tutoring*

4. Is there a **systematic relation** between **tutoring-induced neuroplasticity** and behavioral improvement, if any, in DD?

   *Yes, the degree of neuroplasticity* was significantly *related* to **individual differences in performance gain** after tutoring **in DD**
Introduction

- DD often persists into adulthood

- **Learners** diagnosed with DD at age 11, over 40% were still in the DD category at age 17 *(Shalev et al., 2005)*

- High IQ, verbal and memory abilities could help these individual progress through education, yet the social outcome of adult DD is as severe and equally alarming as it often manifests in every day life situations.

- **Check bills**
  - Decide if something is too heavy

- **Pick the right type of mortgage**
  - Talk about prices

- **Remember PIN numbers**
  - Catch the right bus

Gerardi et al., 2013, PNAS
Math-based intervention during the early school years is effective, but in adults with DD such type of intervention is (i) unfeasible; (ii) likely ineffective as brain circuits might have re-organized differently after many years of “bad math”
tDCS

Neuro-modulation technique

Low-amplitude direct currents – applied via scalp electrodes – act on polarization-dependent mechanisms of resting membrane potential.

**Anodal stimulation** increases excitability by pushing neural resting membrane potentials closer to the activation threshold.

**Cathodal stimulation** – the reverse polarity – inhibits cell firing and decreases excitability.
Transcranial Direct Current Stimulation for Refractory Auditory Hallucinations in Schizophrenia
Chittaranjan Andrade, MD

Modulating Neuronal Activity Produces Specific and Long-Lasting Changes in Numerical Competence

Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory

Transcranial Direct Current Stimulation (tDCS) Decreases Abnormalities of Long-Latency Stretch Reflexes in Cerebellar Ataxia
Giuliana Grimaldi and Mario Manto

Transcranial Direct Current Stimulation for Major Depression: A General System for Quantifying Transcranial Electrotherapy Dosage
Marom Bikson, PhD
Peter Bifulco, MD, MFA

Efficacy of semantic–phonological treatment combined with tDCS for verb retrieval in a patient with aphasia
Rosa Manenti, Michela Petesi, Michela Brambilla, Sandra Rosini, Antonio Miozzo, Alessandro Padovani, Carlo Minissi, and Maria Cotelli

Studying direct current stimulation for refractory auditory hallucinations in schizophrenia:

Comparing immediate transient tinnitus suppression using tACS and tDCS: a placebo-controlled study
Sven Vanneste, Vincent Walsh, Paul Van De Heyning, Dirk De Ridder

Effect of a tDCS electrode montage on implicit motor sequence learning in healthy subject
Eun Kyong Kang and Nam-Jong Paik

Research Article

Report

Current Biology 20, 1–5, November 23, 2010

doi:10.1016/j.cub.2010.10.012

DOI 10.1007/s00221-013-3406-7
Could numerical abilities in persistent DD be effectively modulated by the application of neuro-modulation techniques – such as tDCS – applied together with a learning paradigm?
## Methods and Material

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\(^a\) RD included; \(^b\) FTD included; \(^c\) DHI included; \(^d\) RSH included.
# Methods and Material

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## Domain-General Assessments

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<td>Performance IQ</td>
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## Visuo-Spatial Skills-WAIS

- Block design: 13, 15

## Domain-Specific Assessments

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<tr>
<td>WF</td>
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**Arithmetic test - WAIS**

- Arithmetic: 50%ile, 50%ile

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Iuculano & Cohen Kadosh, 2013

**Artificial digits**

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Learning task
Correct
Mistake
Methods and Material

I. tDcS was delivered for 20 min from the start of the training

The training continued after the termination of the stimulation

II. Once the training ended, the subject performed a Numerical Stroop task

III. and a Number Line task

III.
tDCS - Montage

**DD1**

- RA-LC

**DD2**

- LA-RC

Iuculano & Cohen Kadosh, 2013
Results – Learning curves

Equivalent fit for both DD1 and DD2

Performance of both DDs was also equivalent to healthy controls
Results – Numerical Stroop task

DD2 exhibited the canonical Congruency effect (Congruent > Neutral > Incongruent).
DD1’s performance was not modulated by numerical information (Neutral > Congruent).

DD2 showed a Congruency effect related to the numerical distance between stimuli; while for DD1 the Neutral condition was always the easiest.
Results – Number Line task

- DD2 showed a linear fit in mapping the artificial digits
- DD1 did not
Could numerical abilities in persistent DD be effectively modulated by the application of neuro-modulation techniques – such as tDCS – applied together with a learning paradigm?

Yes, neuromodulation techniques accompanied by learning paradigms could be effective in remediating performance in adults with DD

**Successful tDCS montage for DD**

![Successful tDCS montage for DD](image)

**Successful tDCS montage for healthy adults**

![Successful tDCS montage for healthy adults](image)

This could reflect: (i) variability between DD cases both in terms of performance as well as brain morphology – need for ad-hoc stimulation (?)

(ii) neural-reorganization/plasticity effects reflected by inter-hemispheric compensation → tDCS might up-regulate the excitability of the compensatory mechanisms while down-regulating the impaired contro-lateral area
Conclusions

• **Brain-based measures** can provide a sensitive **biomarker** for diagnosis as well as response to treatment for DD

• **The unique contribution** of **neuroscience-based approaches** to guide intervention practice in DD, pointing to specific **brain systems** that can be fruitfully **targeted** for improving skills of **weak-responders**
The Stanford Cognitive and Systems Neuroscience Laboratory

The kids and their families

Dr. Roi Cohen Kadosh
Funding Sources

- National Institutes of Health
- Stanford Institute for Neuroscience
- Singer Foundation

Thank you
Training the “Mathematical Brain”: evidence from functional brain imaging and neuro-modulation techniques
Extra Slides
Results – ANOVA model

Group by Session Interaction

- Prefrontal Cortex
  - L DLPFC
  - R DLPFC
  - y = 50

- Parietal Cortex
  - L VLPFC
  - L AIC
  - R AIC
  - L IPS
  - z = -6

- Ventral Temporal Occipital Cortex
  - L IPS
  - L FG
  - z = -24

- Medial Temporal Lobe
  - L Hippocampus
  - y = -16
Results – Control analyses – *FIQ scores*

Between group differences controlling for FIQ

**A**

DD > TD

- **Pre Tutoring**
  - Prefrontal Cortex
  - Parietal Cortex
  - Ventral Temporal Occipital Cortex
  - Medial Temporal Lobe

**B**

DD > TD

- **Post Tutoring**

- *y* = 38
- *z* = -9
- *y* = -58
- *z* = -16
- *y* = -16
Results – Control analyses – *PIQ scores*

Between group differences controlling for PIQ

A. DD > TD

Pre Tutoring

Prefrontal Cortex

Parietal Cortex

Ventral Temporal Occipital Cortex

Medial Temporal Lobe

B. DD > TD

Post Tutoring

y = 46  z = -8  y = -58  z = -16  y = -16

Iuculano et al., under review
Results – Control analyses – Reading scores

Between group differences controlling for Reading scores

A

DD > TD

Prefrontal Cortex

L DLPFC

LAIC

L VLPFC

Parietal Cortex

L IPS

R AIC

Ventral Temporal Occipital Cortex

R FG

Medial Temporal Lobe

L Hippocampus

Pre Tutoring

B

DD > TD

y = 50

z = -9

y = -58

z = -16

y = -16

Post Tutoring
Before tutoring children with DD showed **over-activation** in multiple brain areas of the PFC, PPC, VTOC and MTL, compared to TD children.

After tutoring **no differences** were evident between DD children and their TD control peers.
Results – TD children – Post > Pre

**Figure S2** – Within group analyses. (C) TD: No brain areas showed higher activation levels before, compared to after, tutoring; (D) After 8-weeks tutoring TD showed increased activation levels in areas of the parietal cortex and MTL.

Before tutoring children with TD showed **over-activation** in multiple brain areas of the PFC, PPC, VTOC and MTL, compared to TD children

After tutoring no differences were evident between DD children and their TD control peers
Multivariate pattern analysis

fMRI during math problem solving

Brain activation maps

Multivariate pattern analysis

Brain areas that show differences in multivariate brain activity patterns between ASD and TD

Test on Left Out Participants’ maps

ASD or TD?

Train on individual participants’ patterns of brain activity

Abrams et al., 2013; Cho et al., 2011; Iuculano et al., 2014; Uddin et al., 2011. 2013
tDCS

DC current applied via pair of electrodes; current induced in conductor

Anodal stimulation to the PPC improves numerical skills

**Study 2**

![Graph A](image)

- Reaction time (in ms)
- Congruent (black), Neutral (dark gray), Incongruent (light gray)
- Conditions: Sham, RC-LA, RA-LC

![Graph B](image)

- Cumulative effect (in ms)
- Conditions: Sham, RC-LA, RA-LC

![Graph C](image)

- Reaction time (in ms)
- Conditions: Sham, RC-LA, RA-LC

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<td>47</td>
<td>35</td>
</tr>
</tbody>
</table>
Anodal stimulation to the PPC improves numerical skills

Study 2

Cohen Kadosh et al., 2010
Neuro-modulation technique

Low-amplitude direct currents – applied via scalp electrodes - modify transmembrane neuronal potential (depolarize or hyperpolarize) thus influencing the level of excitability by modulating the firing rate of individual neurons